ATCC No. 39,709, and those sequences have fewer than 29 amino acids deleted from their C-terminuses. (TX 135, D.I. 122 at A-8357; TX 201, D.I. 122 at A-8531; Jorgensen, Tr. at 661:15-663:7.) However, those sequences were not determined from samples of G997 alpha-amylase as sold by Defendants, and so the sequences do not demonstrate variations in G997. While the sequences reflected in exhibits TX 135 and TX 201 have different C-terminal endings than the sequence in TX 226, those differences apparently reflect variations in conditions of protein expression, including the organism in which the protein is produced. (Jorgensen, Tr. at 663:8-16, 664:9-15.)

69. In sum, the preponderance of the evidence shows that there is one sequence for G997: the one reported in TX 226. I conclude that TX 226 accurately states the sequence of G997.

III. CONCLUSIONS OF LAW

1. Jurisdiction over the subject matter of this action is proper under 28 U.S.C. §§ 1331 and 1338.

A. *Claim Construction*

2. A patent infringement analysis involves two steps: claim construction and the application of the construed claim to the accused process or product. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). To allow the trial to be held on an expedited basis, I bifurcated this case and combined the claim construction hearing and liability phase of the trial. (*See* 10/19/05 preliminary injunction hearing transcript at 65.)

3. Patent claims are construed as a matter of law. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454-56 (Fed. Cir. 1998) (en banc). "[T]he words of a claim 'are generally given their ordinary and customary meaning.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). That ordinary meaning "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1313.

4. To determine the ordinary meaning of a term, the court should review "the same resources as would" the person of ordinary skill in the art. *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998). Those resources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004).

5. "[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms." *Phillips*, 415 F.3d at 1314. Both "the context in which a term is used in the asserted claim" and the "[o]ther claims of the patent in question" are useful for understanding the ordinary meaning. *Id*.

6. "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id*. at 1315 (quoting *Vitronics*, 90 F.3d at 1582). In short, the claims "must be read in view of the specification, of which they are a part." *Markman*, 52 F.3d

at 979. Thus, "[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

7. On occasion, "the specification may reveal a special definition given to a claim term . . . that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316 (citing *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). The specification may also "reveal an intentional disclaimer, or disavowal, of claim scope by the inventor . . . [which] is regarded as dispositive." *Id.* (citing *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1343-44 (Fed. Cir. 2001)).

8. The court "should also consider the patent's prosecution history." *Markman*, 52 F.3d at 980. "Like the specification, the prosecution history provides evidence of how the [Patent and Trademark Office] and the inventor understood the patent." *Phillips*, 415 F.3d at 1317 (citing *Lemelson v. Gen. Mills, Inc.*, 968 F.2d 1202, 1206 (Fed. Cir. 1992)).

9. The court may rely on extrinsic evidence, which is "all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. In particular, "dictionaries, and especially technical dictionaries, . . . have been properly recognized as among the many tools that can assist the court in determining the meaning of particular terminology." *Phillips*, 415 F.3d at 1318 (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*,

299 F.3d 1313, 1325 (Fed. Cir. 2002)). However, extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004) (quoting *Vanderlande Indus. Nederland BV v. Int'l Trade Comm'n*, 366 F.3d 1311, 1318 (Fed. Cir. 2004)).

10. During claim construction, "[t]he sequence of steps used by the judge in consulting various sources is not important; what matters is for the court to attach the appropriate weight to be assigned to those sources in light of the statutes and policies that inform patent law." *Phillips*, 415 F.3d at 1324.

11. Here, the parties agree about the meaning of the terms "variant," which is used in claims 1, 3, and 5, and "parent," which is used in claim 1. A variant is a protein that has been derived from a parent protein by protein engineering, so that there are substitutions, insertions, or deletions of amino acids in the variant relative to the parent. ('031 patent, 3:59-67; Arnold, Tr. at 137:23-138:9; Alber, Tr. at 202:8-11.)

12. The parties dispute the meaning of two claim terms: *"Bacillus stearothermophilus* alpha-amylase," which is used in claims 1 and 5, and "% homology," which is used in claims 1 and 3.

1. *"Bacillus stearothermophilus Alpha-Amylase"*

a. *The Parties' Proposed Constructions*

13. Novozymes contends that a *Bacillus stearothermophilus* alpha-amylase is "the functional enzyme product that is produced from the alpha-amylase gene of a *Bacillus stearothermophilus* organism." (D.I. 118 at 18.)

14. Defendants propose two constructions of the term. First, they argue that the '031 patent prosecution history shows that the applicants defined *Bacillus stearothermophilus* alpha-amylase as "an alpha-amylase having the amino acid sequence of SEQ ID NO:3." (D.I. 116 at 5.) Alternatively, they argue that a person having ordinary skill in the art would understand that a *Bacillus stearothermophilus* alpha-amylase is "a 514- or 515-amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene, minus the signal sequence." (*Id*. at 8-9.)

15. The parties at least agree with the starting proposition that a *Bacillus stearothermophilus* alpha-amylase is produced from a gene taken from a *Bacillus stearothermophilus* bacterium. The narrowing constructions proposed by Defendants require that the alpha-amylase have either a particular sequence or a particular length.

b. *The Court's Construction*

16. I conclude that Novozymes's construction is the correct one. Neither the prosecution history nor the evidence concerning the expected length of an alpha-amylase supports the adoption of the narrower constructions proposed by Defendants.

i. *The Term is Not Limited to SEQ ID NO:3*

17. Defendants' argument for their first proposed construction is based on the prosecution history of the '031 patent, specifically, the applicants' response to the examiner's written description and enablement rejections. (D.I. 116 at 5-8.)

18. In the first office action, when the examiner issued rejections for failure to satisfy the written description and enablement requirements, she suggested that the rejections could be overcome by amending the claims to require "at least 80% identity"

between the variant and SEQ ID NO:3. (FF ¶ 29.) In their response, the applicants did not make the suggested change, and instead amended the claims to require "at least 80% homology" between the variant and the parent *Bacillus stearothermophilus* alpha-amylase. (FF ¶ 37.) In the second office action, the examiner, upon further consideration, again rejected the claims, and suggested that the rejections could be overcome by requiring "at least 90% identity" between the variant and SEQ ID NO:3. (FF ¶ 41.) The applicants responded by canceling the claims and adding new claims that required "at least 95% homology" between the variant and the parent *Bacillus stearothermophilus* alpha-amylase. (FF ¶ 50.) In support of those new claims, the applicants noted the examiner's suggestion that the variants have 90% homology to SEQ ID NO:3 and argued that the rejection was "rendered moot . . . as the new claims recite a homology of 95%." (*Id.*)

19. According to Defendants, that exchange demonstrates that the applicants and the examiner both understood that the "*Bacillus stearothermophilus* alpha-amylase"[22] was the same as "SEQ ID NO:3." (D.I. 116 at 7-8.) However, the prosecution history establishes that the examiner and the applicants recognized that the terms were not synonymous. In the second office action, the examiner pointed out that

[22]Defendants' argument sometimes purports to construe "parent *Bacillus stearothermophilus* alpha-amylase." (D.I. 116 at 7-8.) I understand it to be an argument about the construction of "*Bacillus stearothermophilus* alpha-amylase," because Defendants seek to apply the construction to claim 5 (*id.* at 8, 18-19), which does not contain the term "parent," and because Defendants assert that there is no dispute about the construction of "parent" (D.I. 115 at 61, ¶ 9). In any case, I conclude that the term "parent," as used in claim 1, is properly construed as the protein from which the variant is derived, and that the term "parent" does not alter the meaning of "parent *Bacillus stearothermophilus* alpha-amylase" in a way that is relevant to the parties' dispute.

the applicants had not adopted her suggestion, but that the amendments were "similar." (FF ¶ 40.) In their response to the second office action, the applicants stated that their invention was "directed to variants of *Bacillus stearothermophilus* alpha-amylase enzymes and to alpha-amylase variants having 95% homology to SEQ ID NO:3." (TX 101, D.I. 121 at A-7736.) The applicants also stated that the specification described "variants of *Bacillus stearothermophilus* and variants having at least 95% homology to SEQ ID NO:3." (*Id.* at A-7735.) Those statements describe two different sets of variants, those defined relative to *Bacillus stearothermophilus* alpha-amylase and those defined relative to SEQ ID NO:3. Thus, contrary to Defendants' argument (D.I. 116 at 7-8), the record shows that the examiner and applicants understood that "SEQ ID NO:3" was not used interchangeably with "*Bacillus stearothermophilus* alpha-amylase" or "parent *Bacillus stearothermophilus* alpha-amylase." That record is also consistent with the claims: claims 1 and 5 refer to a "*Bacillus stearothermophilus* alpha-amylase," and claim 3 refers to "SEQ ID NO:3." ('031 patent, 65:11-17, 65:21-66:12, 66:16-19.)

20. Therefore, the term "*Bacillus stearothermophilus* alpha-amylase" is not limited to SEQ ID NO:3.

ii. *The Term is Not Limited to Proteins of a Particular Length*

21. Defendants' argument for their second proposed construction is based on the examples in the '031 patent and on extrinsic evidence about alpha-amylases.

22. First, Defendants note that the examples of *Bacillus stearothermophilus* alpha-amylases disclosed in the patent have either 514 or 515 amino acids. (D.I. 116 at 9 (citing '031 patent, Fig. 1, 7:32-35, sequence listing for SEQ ID NO:3).)

23. Second, Defendants emphasize extrinsic evidence to show that, at the patent's critical date in 1995, *Bacillus stearothermophilus* alpha-amylases would have been expected to have 514 or 515 amino acids after the removal of the N-terminal signal sequences. (Alber, Tr. at 209:2-18, 209:25-210:5, 211:6-212:3, 212:19-214:8; TX 142; TX 568; TX 628; TX 629; TX 630; TX 633; TX 634; TX 635.) According to Defendants, that information means that, by definition, a "*Bacillus stearothermophilus* alpha-amylase" must be 514 or 515 amino acids in length. (D.I. 116 at 9-10.)

24. I disagree with Defendants' conclusion that length is a defining feature of *Bacillus stearothermophilus* alpha-amylases. First, none of the evidence adduced by Defendants reports the complete, experimentally determined amino acid sequence of an alpha-amylase. Instead, that evidence shows the results of DNA sequencing of genes, alone (TX 142; TX 629; TX 630; TX 666) or in combination with amino acid sequencing of the N-terminus of the protein (TX 568; TX 628; TX 634; TX 666), and the results of gel electrophoresis experiments (TX 633; TX 635). That evidence may lead to the expectation that, if one were to do the experiment, an alpha-amylase would have a precise length of 514 or 515 amino acids. However, in 1995 the experiment remained to be done.

25. Second, even if Defendants had shown that all *Bacillus stearothermophilus* alpha-amylases had a specific length—which they have not shown—none of the evidence, including the '031 patent itself, dictates that a *Bacillus stearothermophilus* alpha-amylase must have a particular length. The fact that examples in the patent have a given length is not sufficient to make that length a

defining feature of *Bacillus stearothermophilus* alpha-amylases. I conclude that a person having ordinary skill in the art would not understand the '031 patent to impose such a length requirement.

26. Therefore, the term "*Bacillus stearothermophilus* alpha-amylase" is not limited to proteins having 514 or 515 amino acids.

27. Accordingly, I conclude that the construction proposed by Novozymes is correct. A *Bacillus stearothermophilus* alpha-amylase is "the functional enzyme product that is produced from the alpha-amylase gene of a *Bacillus stearothermophilus* organism."

2. *"% Homology"*

a. *The Parties' Proposed Constructions*

28. Novozymes proposes that "% homology" means "a percent identity calculation according to the standard whereby the number of exactly matching amino acid residues in two sequences is compared to the total number of residue positions that are present in both sequences, expressed as a percent, e.g., as implemented by the GAP GCG program." (D.I. 118 at 19.)

29. Defendants argue that the calculation of homology "requires use of any method that accounts for all substitutions, insertions, and deletions, including internal and terminal deletions, over the entire amino acid sequences of the variant and parent alpha-amylases identified in the claims." (D.I. 115 at 63, ¶ 16.) That calculation is not consistent with Novozymes's proposed construction, primarily because Novozymes's calculation method does not count deletions.

b. *The Court's Construction*

30. Because Novozymes's proposed construction is consistent with unambiguous instructions given in the '031 patent, I conclude that it is the correct construction.

31. According to the patent:

> An amino acid sequence is considered to be X % homologous to the parent α-amylase if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in *Science* 227 (1985) p. 1435, reveals an identity of X %. The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used, employing default values for GAP penalties [Genetic Computer Group (1991) Programme Manual for the GCG Package, version 7, 575 Science Drive, Madison, Wis., USA 53711].

('031 patent, 4:36-45.) Thus, according to that passage, "% homology" is equivalent to percent identity. (Devereux, Tr. at 124:22-25, 128:9-13; Arnold, Tr. at 140:6-14; Alber, Tr. at 294:5-9.) Also, the passage sets forth a methodology that, first, aligns the sequences and, second, calculates the percent identity from the alignment. (Devereux, Tr. at 126:9-12; Arnold, Tr. at 145:14-20; Alber, Tr. at 233:22-24.) Finally, a software package is suggested that "may suitably be used" to perform the alignment and calculation of identity.

32. Novozymes's construction is based on the methodology used by that software package. In the GAP program, identity is calculated by counting the number of exact matches of amino acid residues between two aligned sequences and dividing by the number of positions where there are residues present in both sequences. (Devereux, Tr. at 109:22-110:6.) When one sequence has a residue with no corresponding residue in the other sequence, the program allows a gap in the

alignment, and that position is not counted in the denominator of the identity calculation. (*Id*. at 109:13-21, 110:7-111:12.)

33. Defendants argue that even though the patent states that GAP is suitable for the calculation, a person having ordinary skill in the art would understand that using GAP would be incorrect. (D.I. 116 at 11-14.) First, Defendants note that while GAP "may suitably be used," it is not required, and that other methods for doing the calculation were available when the specification was written, methods that might give a different result. (*Id*. at 11-12 (citing Arnold, Tr. at 181:12-182:10, 190:19-191:3; Alber, Tr. at 234:25-235:8).)

34. Second, Defendants argue (D.I. 116 at 13-14) that the '031 specification teaches that deletions, which will cause gaps in an alignment, are important modifications that can be made by protein engineers. Indeed, the patent includes deletions in its general description of possible modifications ('031 patent, 3:59-65) and the claims themselves require deletions at positions 179 and 180 (*id*., 65:11-17, 65:21-66:12, 66:16-19). In addition, Defendants cite extrinsic evidence to support the proposition that a person having ordinary skill in the art would understand that deletions were important in the field of protein engineering. (TX 511, D.I. 122 at A-8886, ¶ 30; Alber, Tr. at 216:9-217:6, 217:20-218:20.) Because of that importance, Defendants contend, those skilled in the art would know that deletions should be included in the calculation of percent identity.

35. While I agree that the '031 patent discloses that deletions are relevant modifications, those general statements, which are not made in the context of a discussion of percent identity, are not sufficient to overcome the express instruction that

GAP may suitably be used. Indeed, the presence of both the commentary on deletions and the instruction regarding GAP shows that the patentee gave the instructions with full understanding about the importance of deletions. It was no oversight or mistake. While the patent does not instruct that GAP is the only way to do the calculation, that does not imply, as Defendants suggest, that GAP should not be used. A construction that requires that GAP not be used would be contrary to the express language of the patent.

36. I conclude that the construction proposed by Novozymes is correct, because it is consistent with those unambiguous instructions in the patent. "% homology" means "a percent identity calculation according to the standard whereby the number of exactly matching amino acid residues in two sequences is compared to the total number of residue positions that are present in both sequences, expressed as a percent, e.g., as implemented by the GAP GCG program."

B. *Infringement*

37. The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001) (Patent infringement, "whether literal or under the doctrine of equivalents, is a question of fact."). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Envirotech*

Corp. v. Al George, Inc., 730 F.2d 753, 758 (Fed. Cir. 1984) (citing *Hughes Aircraft Co. v. United States,* 717 F.2d 1351, 1361 (Fed. Cir. 1983)).

38. I conclude that Spezyme Ethyl literally infringes claims 1, 3, and 5 of the '031 patent.

1. *Claim 1*

39. Claim 1 of the '031 patent claims a variant of a parent *Bacillus stearothermophilus* alpha-amylase. A variant is a protein that has been derived from a parent protein by protein engineering, so that there are substitutions, insertions, or deletions of amino acids in the variant relative to the parent. (Conclusion of Law ["CL"] ¶ 11.) Spezyme Ethyl is a protein that has been derived from the gene that codes for G997. (TX 194, D.I. 122 at A-8525.) As described below, Spezyme Ethyl contains deletions of two amino acids relative to G997. (CL ¶ 42.) Therefore, I conclude that Spezyme Ethyl is a variant of the parent, G997.

40. I also conclude that G997 is a *Bacillus stearothermophilus* alpha-amylase, because it is the functional enzyme product that is produced from the alpha-amylase gene of a *Bacillus stearothermophilus* organism. (Alber, Tr. at 258:2-259:3.) While Defendants argue that G997 cannot be a *Bacillus stearothermophilus* alpha-amylase because there is no single protein sequence for G997 (D.I. 116 at 10-11, 19-20), I have concluded to the contrary that the sequence set forth in TX 226 is, in fact, the sequence of G997 (FF ¶ 69).

41. Claim 1 further requires the variant to have at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and to comprise a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering.

42. The parties do not dispute the sequence alignment of Spezyme Ethyl and G997. (Alber, Tr. at 299:2-7.) When the sequences are aligned and the GAP program is used to calculate percent homology (identity), Spezyme Ethyl has 100% homology to G997, and the amino acids corresponding to positions 179 and 180 in SEQ ID NO:3 have been deleted in Spezyme Ethyl.[23] (TX 126, D.I. 122 at A-8347-48; Devereux, Tr. at 112:22-113:20, 115:18-22.) Therefore, Spezyme Ethyl has at least 95% homology to G997, and Spezyme Ethyl comprises a deletion of amino acids 179 and 180.

43. Finally, claim 1 requires the variant to have alpha-amylase activity. Defendants do not dispute that Spezyme Ethyl has alpha-amylase activity. (TX 194, D.I. 122 at A-8525; TX 134, D.I. 122 at A-8355.)

44. Because each and every element set forth in claim 1 is found in Spezyme Ethyl, it literally infringes claim 1.

2. *Claim 3*

45. Claim 3 of the '031 patent claims a variant that has at least 95% homology to SEQ ID NO:3, that comprises a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering, and that has alpha-amylase activity.

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[23]According to my construction, the calculation of "% homology" does not account for gaps (CL ¶¶ 30-36), so the deletion of amino acids 179 and 180 does not affect the 100% homology between Spezyme Ethyl and G997.

46. Spezyme Ethyl is a variant (CL ¶ 39), and it has alpha-amylase activity (CL ¶ 43).

47. The parties do not dispute the sequence alignment of Spezyme Ethyl and SEQ ID NO:3. (Alber, Tr. at 299:2-7.) When the sequences are aligned and the GAP program is used to calculate percent homology (identity), Spezyme Ethyl has 98.967% homology to SEQ ID NO:3, and the amino acids corresponding to positions 179 and 180 in SEQ ID NO:3 have been deleted in Spezyme Ethyl. (TX 127, D.I. 122 at A-8349-50; Devereux, Tr. at 117:22-118:16.) Therefore, Spezyme Ethyl has at least 95% homology to SEQ ID NO:3, and Spezyme Ethyl comprises a deletion of amino acids 179 and 180.

48. Because each and every element set forth in claim 3 is found in Spezyme Ethyl, it literally infringes claim 3.

3. *Claim 5*

49. Claim 5 of the '031 patent claims a variant of a *Bacillus stearothermophilus* alpha-amylase that consists of a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering.

50. Spezyme Ethyl is a variant of G997 (CL ¶ 39), and the only difference between Spezyme Ethyl and G997, as shown by their sequence alignment (TX 126, D.I. 122 at A-8347-48) is the deletion of residues 179 and 180. (Arnold, Tr. at 146:12-23.)

51. Because each and every element set forth in claim 5 is found in Spezyme Ethyl, it literally infringes claim 5.

C. *Invalidity*

52. When a party challenges a patent's validity, the starting point for analyzing that challenge is the statutory presumption of validity. *See* 35 U.S.C. § 282 ("A patent shall be presumed valid."). Accordingly, "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." *Id.* Invalidity must be shown by clear and convincing evidence. *Robotic Vision Sys. v. View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999). This presumption of validity is never weakened, and the burden of proving invalidity does not shift from the party asserting invalidity. *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 745 F. Supp. 998, 1004 (D. Del. 1990) (citing *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1574-75 (Fed. Cir. 1984) (other citations omitted)). The burden of going forward with evidence rebutting invalidity may shift to the patentee only after the party asserting invalidity has demonstrated a legally sufficient prima facie case of invalidity. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 291 (Fed. Cir. 1985) (internal citations omitted). If the party asserting invalidity has established a legally sufficient case of invalidity, the court then examines all of the evidence of invalidity together with all of the evidence rebutting invalidity, and determines whether there is clear and convincing evidence of invalidity. *Id*. at 291-92.

53. Defendants challenge the validity of the '031 patent on two grounds: obviousness and lack of enablement.

1. *Obviousness*

54. An invention is unpatentable if "the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005). In determining whether an invention is obvious, the court should consider: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective indicia of nonobviousness. *See id.* at 1372-73 (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

55. A prima facie case of obviousness is established by showing that a combination of references contains every limitation of the claims-at-issue, and that the prior art would motivate a person having ordinary skill in the art to combine the references and would suggest a reasonable likelihood of success. *Smiths Indus. Med. Sys., Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1353 (Fed. Cir. 1999).

56. Objective evidence of nonobviousness includes evidence of unexpected results. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Results are unexpected when "the claimed invention exhibits some superior property or advantage that a person in the relevant art would have found surprising or unexpected." *Id.* Such results must be unexpected as compared to the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

57. Defendants argue that claims 1, 3, and 5 of the '031 patent are obvious both in light of the Suzuki reference combined with the Bisgård-Frantzen reference and in light of the Machius reference alone. I conclude that Defendants have not shown by clear and convincing evidence that the claims are obvious in the face of Novozymes's evidence of unexpected results.

a. *Suzuki and Bisgård-Frantzen*

58. The Suzuki reference disclosed alpha-amylases from *Bacillus amyloliquefaciens* that were modified by the deletion of two amino acids at positions 176 and 177 and that had improved thermostability. (FF ¶ 31.)

59. The Bisgård-Frantzen reference disclosed that the alpha-amylases of *Bacillus amyloliquefaciens*, *Bacillus stearothermophilus*, and *Bacillus licheniformis* were highly similar and that positions 176 and 177 of the *Bacillus amyloliquefaciens* enzyme corresponds to positions 179 and 180 of the *Bacillus stearothermophilus* enzyme. (FF ¶ 32.)

60. The Defendants succeeded in making a prima facie showing that claims 1, 3, and 5 are obvious in light of Suzuki and Bisgård-Frantzen. As the examiner noted during prosecution (FF ¶ 33), the combination of those references discloses a *Bacillus stearothermophilus* alpha-amylase with deletions at positions 179 and 180, and a person having ordinary skill in the art would have been motivated to make the claimed deletions to increase thermostability, with a reasonable expectation of success.

61. While Novozymes argues (D.I. 125 at 21-22) that there would have been no expectation of success, the evidence used to support that proposition shows that

there would have been an expectation, but no guarantee, of improvement in thermostability, although the magnitude of that improvement would have been uncertain. (Arnold, Tr. at 742:9-12; Machius, Tr. at 490:21-491:4, 508:15-23; Zeikus,[24] Tr. at 699:8-12.)[25] I conclude that there would have been a reasonable expectation of success based on the sequence similarity between the alpha-amylases from *Bacillus amyloliquefaciens* and *Bacillus stearothermophilus* reported by Bisgård-Frantzen.

62. Because I conclude that there is prima facie obviousness, I next consider Novozymes's rebuttal evidence, which was presented to the examiner and purports to show that the invention of the '031 patent gives unexpected results. By presenting that evidence at trial, Novozymes has met its burden of production of evidence to rebut the prima facie case for obviousness. Defendants challenge that evidence, and, as the parties asserting invalidity, must prove by clear and convincing evidence the facts that support the ultimate conclusion of obviousness. *Ashland Oil*, 776 F.2d at 291-92.

b. *Unexpected Results*

63. The examiner found that the Borchert Declaration showed unexpected results sufficient to overcome an obviousness rejection based on Suzuki and Bisgård-Frantzen. (FF ¶ 51.) Defendants argue that the Borchert Declaration does not demonstrate unexpected results, because (1) the Borchert experiment did not measure

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[24]Dr. Gregory Zeikus, who submitted a declaration in support of Defendants' opposition to Novozymes's motion for a preliminary injunction (D.I. 40), testified at trial by deposition.

[25]The testimony of Dr. Arnold and Dr. Machius that Novozymes cites refers to the expectation of success based on the Machius reference, not on Suzuki and Bisgård-Frantzen, and the testimony of Dr. Zeikus apparently refers to the expectation of success based on Suzuki alone.

thermostability under the conditions reported by Suzuki, (2) the experimental procedures were so deficient that the results are not reliable evidence of anything, and (3) the results, taken at face value, were not unexpected. (D.I. 116 at 21-22.) I conclude that Defendants have failed to show by clear and convincing evidence that the Borchert Declaration results are unfair, unreliable, or not unexpected.

i. *Suzuki Conditions*

64. The experiment reported in the Borchert Declaration (the "Borchert experiment") compared *Bacillus stearothermophilus* alpha-amylases with the alpha-amylases reported by Suzuki.

65. According to Defendants, the Borchert Declaration is an unfair comparison to Suzuki because the experimental conditions of Suzuki were modified. (*Id.* at 21.) First, Suzuki tested thermostability of alpha-amylases at 90°C (TX 115, D.I. 122 at A-8237), and the Borchert experiment tested thermostability at 80°C (FF ¶ 44). Second, Suzuki used buffer containing 10 mM calcium (TX 115, D.I. 122 at A-8234), and the Borchert experiment used buffer containing 0.1 mM calcium (FF ¶ 44). Third, Suzuki preheated the buffer prior to adding the alpha-amylase, in order to avoid the effects of a "ramp-up period," i.e., a time delay in the enzyme reaching the incubation temperature. (TX 115, D.I. 122 at A-8234; Klibanov, Tr. at 514:14-24.) The Borchert experiment did not preheat the buffer. (Borchert, Tr. at 397:4-7.) Defendants contend that the conditions of the Borchert experiment unfairly enhanced the relative improvement of BSG compared to BAN.[26] (D.I. 116 at 21.)

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[26]Again, the Borchert experiment measured thermostability for *Bacillus amyloliquefaciens* alpha-amylase with and without the deletion ("BAN" and "BANdel")

66. If Suzuki is indeed the closest prior art, as the applicants believed, then the showing of unexpected results must compare the effect of the claimed deletion in BSG to the effect of the deletion in BAN reported by Suzuki. Such a comparison might be made in two ways. First, the applicants might have measured thermostability only for BSG alpha-amylases and then compared those results to those reported by Suzuki for BAN. For such a comparison between the results of two separate experiments to be fair, the conditions of the two experiments would have to be the same. Second, the relative improvement in BSG might be determined by actually making measurements for both BSG and BAN under identical conditions. That experiment would be a fair comparison of the improvement in thermostability of BSG and BAN under the conditions of the experiment. The applicants chose the second way to make the comparison. Except for the ramp-up period issue, which is discussed further below (CL ¶¶ 67, 70), Defendants have no credible argument that any valid measurement of thermostability must be done under the same conditions as existed for the Suzuki experiment. Because the Borchert experiment actually conducted side-by-side experiments to measure the thermostability of BAN and BSG under identical conditions, those experiments are a fair comparison between BAN and BSG under those conditions. Defendants have failed to present clear and convincing evidence showing otherwise.

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and for *Bacillus stearothermophilus* alpha-amylase with and without the deletion ("BSG" and "BSGdel"). (FF ¶¶ 43-44.)

ii. *Experimental Procedures*

67. Defendants also argue that the procedures used in the Borchert experiment were faulty, making the results unreliable and leaving Novozymes without any evidence of unexpected results. (D.I. 116 at 22.) First, Defendants point to the failure to account for the ramp-up period. In the experiment, the time measurement for heat inactivation started when the tubes containing buffer with the alpha-amylases were placed in a heating device. Therefore, the alpha-amylases were not actually exposed to a temperature of 80°C for the short time it took for the solution to heat up to that temperature. (Klibanov, Tr. at 523:21-524:11.) Dr. Klibanov testified that the standard protocol for these experiments would avoid the problem by preheating the buffers used in the experiment. (*Id.* at 525:13-526:2.) According to Dr. Klibanov, the failure to account for that ramp-up period would have the largest effect on the half-life calculation for the least stable alpha-amylase, unmodified BAN, and little effect on the other calculated half-lives. (*Id.* at 604:7-605:9.) Thus, according to Defendants, the calculated half-life of unmodified BAN was too high, making the apparent improvement of BANdel too low and the relative improvement of BSGdel too high. (D.I. 115 at 27-28, ¶111 (citing Klibanov, Tr. at 527:18-528:3).)

68. Second, Defendants argue that in order to calculate the half-life of BSGdel, the applicants improperly extrapolated beyond the measured data. (D.I. 116 at 22.) The last activity measurement for BSGdel showed that at 4200 minutes, 61% activity remained. (FF ¶ 45.) Since the activity had not yet fallen below 50%, the half-

life was calculated by assuming that the inactivation followed first order kinetics[27] and extrapolating forward beyond that last data point (Klibanov, Tr. at 531:6-532:1), yielding a calculated half-life of 5775 minutes (FF ¶ 47). According to Dr. Klibanov, the assumption about reaction kinetics was unjustified, making the value of BSGdel unreliable. (Klibanov, Tr. at 533:13-534:5.)

69. Third, Defendants argue that four data points for BSGdel, two at 2881 minutes and two at 2940 minutes, were improperly omitted. (D.I. 115 at 30-32, ¶¶ 121-31.) The measurement for each time point was done in duplicate. (Borchert, Tr. at 395:5-11.) For the two data points at 2881 minutes, Ms. Holbo noticed that the sample from which the measurements were taken had evaporated, and the data were omitted from the half-life calculations. (FF ¶ 46.) According to Dr. Klibanov, Ms. Holbo's explanation was not consistent with the data, because the excluded measurements were lower than expected and, if evaporation had occurred, the enzyme would have become more concentrated and given a higher activity. (Klibanov, Tr. at 537:5-17.) The two data points at 2940 minutes were omitted by Dr. Borchert because the measurements were extremely far apart and one showed activity above 130%. (FF ¶ 46.) Dr. Klibanov agreed that the measurement of 130% could rationally be excluded from the calculation, but he did not agree that excluding the second measurement was justified. (Klibanov, Tr. at 540:9-14.) According to Defendants, the omission of those

[27]A reaction follows first order kinetics if there is a linear relationship between the reaction rate and the concentration of the particular reacting chemical compound. (Klibanov, Tr. at 529:13-17, 532:20-533:5.)

data points led to an overestimate of the half-life of BSGdel. (D.I. 116 at 22; Klibanov, Tr. at 540:9-14.)

70. I conclude that Defendants' criticisms of the Borchert experiment are insufficient to call into question the ultimate conclusion that BSGdel was unexpectedly thermostable. First, as to the ramp-up period, the evidence suggests that for experiments like Borchert's, which used a PCR machine as a heat source and thin plastic tubes to hold the samples, it is not standard protocol to preheat buffer solutions. (Arnold, Tr. at 752:13-754:4.) In addition, in experiments conducted by Novozymes to address the ramp-up issue, the thermostability of BAN was measured with and without preheating the buffer, and the results differed by 15-20%. (*Id*. at 755:18-756:21.) Based on that data, Dr. Arnold concluded that the ramp-up period had "essentially no effect" on the ultimate conclusion of the Borchert experiment. (*Id*. at 757:22-25.) While a 15-20% difference in the BAN half-life would affect the magnitude of the relative improvement reported for BSG, I conclude that that difference is not sufficient to call into question the reliability of Borchert's experiment, which still shows a much greater increase in thermostability for BSG than for BAN. [28]

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[28]The half-life for BAN with preheated buffer was calculated to be 0.469 minutes from that second set of experiments. (Arnold, Tr. at 764:15-24; TX 208R, D.I. 122 at A-8541-42.) Defendants argue that that demonstrates a two-fold effect of the ramp-up period, because that value is about one half as long as that determined by the Borchert experiment (0.9 minutes). (D.I. 115 at 28, ¶ 114.) Even if there were a two-fold effect, the improvement in BSG would still be ~300% of that in BAN, a dramatic improvement. However, I do not agree that Defendants have shown by clear and convincing evidence that there is a two-fold effect. Defendants are comparing the results of two different sets of experiments, and that comparison is inconsistent with the 15-20% effect shown by a comparison of BAN samples with and without preheated buffer in the single set of experiments discussed by Dr. Arnold. That side-by-side comparison of samples from the same set of experiments appears to be a more reliable indicator of the size of the

71. Second, as to the extrapolation problem, Defendants have failed to show that the reported half-life for BSGdel of 5775 minutes is actually far from the truth. Given the measurement of 61% activity at 4200 minutes, it is reasonable to predict a half-life somewhat longer than 4200 minutes. Even if one assumed that after the final measurement at 4200 minutes the activity immediately dropped to zero, taking 4200 minutes as the estimated half-life would give a 46-fold improvement of BSGdel over BSG. (*See* FF ¶ 47 (calculated half-lives).) Such an improvement, which is likely to be an underestimate, would still be unexpected when compared to the 11-fold improvement for BAN.

72. Third, the parties agree that data may properly be excluded if there is a reasonable basis for thinking there is a problem with the experiment. Ms. Holbo decided to exclude two data points at 2881 minutes because the sample had evaporated. There is conflicting expert testimony on whether that was proper. (Klibanov, Tr. at 537:1-17; Arnold, Tr. at 761:7-20.) Given Ms. Holbo's credible testimony that contemporaneous observation indicated something was wrong with the sample, I conclude that there is insufficient evidence to support second-guessing that decision. Dr. Borchert decided to exclude two data points at 2940 minutes based on their measured activities, which were so different from each other that he decided that they were unreliable. Again, experts disagree about whether that was proper. (Klibanov, Tr. at 537:23-538:10; Arnold, Tr. at 758:6-760:5.) And again, I conclude that there is insufficient evidence to support second-guessing that decision.

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ramp-up effect.

73. In sum, Defendants have failed to show by clear and convincing evidence that the results of the Borchert experiment are unreliable.

iii. *Expected Results*

74. Defendants argue that, even if the results in the Borchert Declaration are accepted, the 5.7-fold relative improvement of BSG versus BAN would not be unexpected by a person having ordinary skill in the art. (D.I. 116 at 21-22.) First, Defendants make the intriguing argument that no result could be unexpected because scientists would have had no specific expectation of how the thermostability of BSG would change because of deletions at positions 179 and 180. (D.I. 115 at 32, ¶ 132.) That argument is contrary to the reasoning that supports their prima facie case of obviousness, which rests in part on the assertion that persons of ordinary skill in the art would expect the deletion in BSG to give a similar result to that observed for BAN. By arguing here that no result could be unexpected, no matter what the numerical value, Defendants undercut their argument that the invention is obvious. In any case, the fact that no person having ordinary skill in the art could have predicted a particular numerical value for the improvement does not mean that there was no expectation of improvement. I conclude that, because of the similarity between BAN and BSG, a person having ordinary skill in the art would have expected the deletion to have a similar effect on thermostability, even if the precise magnitude of that effect could not have been predicted. (CL ¶ 61.)

75. Second, Defendants argue that any improvement in the thermostability of BSG would have been expected if it was within an order of magnitude of the 25-fold improvement in BAN reported by Suzuki. (D.I. 115 at 32, ¶ 134.) Thus, the 63-fold

improvement in BSG shown by the Borchert Declaration would not have been unexpected. (*Id.*) While Dr. Klibanov testified to that effect (Klibanov, Tr. at 545:15-546:1, 547:13-549:8), I disagree with Defendants' conclusion. First, the improvement in BAN measured alongside BSG in the Borchert experiment was 11-fold, so the 63-fold improvement in BAN should be compared to that 11-fold improvement rather than the 25-fold improvement from the Suzuki experiment. (*Cf. supra* note 28.) Second, as Dr. Arnold testified, the Borchert experiment shows that making the claimed deletion in BSG yields an enzyme that lasts for days at 80°C. (Arnold, Tr. at 746:24-747:4.) Defendants have not shown that such a result would have been expected by a person having ordinary skill in the art. I conclude that Defendants have failed to show by clear and convincing evidence that the magnitude of the results in the Borchert Declaration were less than unexpected.

76. In sum, Defendants attacks on the fairness, reliability, and unexpectedness of the Borchert Declaration's results fail. Those results must therefore be considered in the determination of the obviousness of claims 1, 3, and 5. While Defendants argue that those unexpected results, even if true, are insufficient to overcome a prima facie showing of obviousness (D.I. 126 at 10-11), I disagree. The sequence similarity between BSG and BAN reported by Bisgård-Frantzen does lead to an expectation of similar effects in those enzymes from the Suzuki deletion. But I agree with the examiner that the dramatic improvement in BSG relative to BAN is sufficiently unexpected to overcome the combination of Suzuki and Bisgård-Frantzen.

77. Therefore, I conclude that Defendants have failed to show that claims 1, 3 and 5 of the '031 patent are obvious over Suzuki and Bisgård-Frantzen.

c. *Machius*

78. Defendants also argue that claims 1, 3, and 5 are obvious in light of the Machius reference alone. (D.I. 116 at 23-26.) For the following reasons, I disagree.

79. Concerning the effect of the deletion of residues 179 and 180, the Machius reference does not disclose much beyond what was already disclosed by Suzuki and Bisgård-Frantzen.[29] The Machius reference shows a sequence alignment that was already available in Bisgård-Frantzen, and it summarizes the improved thermostability reported by Suzuki. (FF ¶¶ 54-55.) The only new information reported by the Machius reference that would affect the expectation of success in making the Suzuki deletion in BSG is the experimental result that the deleted residues are on a surface loop. (FF ¶ 55.) The fact that the residues are on a loop implies that deleting them will not disrupt interactions between amino acids, because surface amino acids have fewer of those interactions. (Machius, Tr. at 774:3-22.)

80. However, while knowing that the amino acids are on a loop might have some effect on the expectation of success, that does not lead logically to the conclusion that the results obtained here were expected. Defendants do not argue that the Machius reference gives any basis for expecting dramatically better thermostability from making the Suzuki deletions in BSG. The Machius reference itself makes no such prediction. (FF ¶ 56.) Thus, the unexpected results reported in the Borchert

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[29]Because the Machius reference discloses very little that is material to the '031 patent claims beyond that reported by Suzuki and Bisgård-Frantzen, I disagree with Defendants' argument (D.I. 116 at 23-24 & n.9) that the Machius reference, rather than Suzuki, is the closest prior art to be compared with the Borchert experiment. In addition, since the Machius reference discloses no experiment on thermostability, it is difficult to see how such a comparison could be made.

Declaration are just as potent for overcoming the Machius reference as they were for Suzuki and Bisgård-Frantzen.

81. Therefore, I conclude that Defendants have failed to show that claims 1, 3 and 5 of the '031 patent are obvious over the Machius reference.[30]

2. *Enablement*

82. Defendants argue that claims 1 and 3 of the '031 patent are invalid because the full scope of those claims is not supported by an enabling disclosure. (D.I. 116 at 26-28.) I conclude that Defendants have failed to show by clear and convincing evidence that the claims are not enabled.

83. To satisfy the enablement requirement, the scope of the claims must bear a reasonable relationship to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). "To be enabling . . . a patent must contain a description that enables one skilled in the art to make and use the claimed invention." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). "That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive." *Id.*

84. Defendants argue that this case is similar to *Amgen*. (D.I. 116 at 26-27.) In *Amgen*, the patent claims at issue covered all DNA sequences suitable for

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[30]In a Memorandum Order dated October 24, 2005 (D.I. 68), I denied Novozymes's motion for a preliminary injunction based Defendants' argument that the asserted claims were obvious in light of the Machius reference. While that argument was sufficient on a preliminary record to show vulnerability and prevent Novozymes from carrying the high burden necessary to get preliminary relief, I now conclude on a complete record that Defendants, who now carry the burden of proof, have failed to show obviousness by clear and convincing evidence.

expression of a protein having at least part of the primary structure and one or more of the biological properties of erythropoietin (EPO). 927 F.2d at 1212-13. The disclosure in that case did not enable one to make all such DNA sequences. *Id*. at 1213-14. While the patent did disclose details of how to make certain EPO analogs, which "might well justify a generic claim encompassing [those] and similar analogs," *id*. at 1213, the disclosure was insufficient to support a claim for "all possible genetic sequences that have EPO-like activity," *id*. at 1214.

85. Here, Defendants note that there are approximately 10^{70} variants that are at least 95% homologous to SEQ ID NO:3 and comprise the double deletion at positions 179 and 180, as required by claim 5. (D.I. 116 at 27 (citing Alber, Tr. at 251:12-17).) For a parent *Bacillus stearothermophilus* alpha-amylase of similar length to SEQ ID NO:3, the number of possible variants with at least 95% homology would apparently be similar. Of those variants, Dr. Alber testified that approximately 1 in 10,000 would have alpha-amylase activity as required by claims 1 and 3. (Alber, Tr. at 252:17-20.) Thus, there are a large number of possible alpha-amylases within the scope of those claims.

86. However, that large number alone is not sufficient to show a lack of enablement in this case. "It is well established that a patent applicant is entitled to claim his invention generically when he describes it sufficiently to meet the [enablement requirement]." *Amgen*, 927 F.2d at 1213. The problem in *Amgen* was that the claim scope covered any gene that could be used to express proteins of various sizes that had one or more of the biological properties of EPO. *Id*. at 1212-13. The Court of

Appeals stated that the disclosure in *Amgen* might well be sufficient to enable a claim for EPO analogs similar to those that were described by the patent. *Id*. at 1213.

87. For claims 1 and 3 of the '031 patent, I conclude that requiring at least 95% homology with either the parent or SEQ ID NO:3 makes the variants sufficiently similar so that the enablement requirement is satisfied. By contrast to *Amgen*, the claim scope here is limited quantitatively to similarity between protein sequences and not just to a requirement for alpha-amylase-like activity. Thus, I agree with the examiner that the 95% homology requirement overcomes the enablement problem in this case. Defendants have failed to show otherwise by clear and convincing evidence.

D. *Unenforceability*

88. Defendants argue that the '031 patent is unenforceable for two reasons: inequitable conduct and prosecution laches.

1. *Inequitable Conduct*

89. Patent applicants have a duty to prosecute applications in the Patent and Trademark Office ("PTO") with candor, good faith, and honesty. *See Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 818 (1945); *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995). This requirement is embodied in 37 C.F.R. § 1.56, which states that "[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section." This duty extends to both applicants and their attorneys. *FMC Corp. v. Manitowoc Co., Inc.*, 835 F.2d 1411,

1415 n.8 (Fed. Cir. 1987) ("'Applicant' as used here includes the patentee and the attorney who prosecuted the application that resulted in the patent-in-suit, because the knowledge and actions of applicant's attorney are chargeable to applicant.").

90. "Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Molins PLC*, 48 F.3d at 1178.

91. A party alleging inequitable conduct must prove it by clear and convincing evidence. *Molins PLC*, 48 F.3d at 1178.

92. To prove inequitable conduct from a failure to disclose material prior art, a party "must offer clear and convincing proof of: (1) prior art or information that is material; (2) knowledge chargeable to applicant of that prior art or information and of its materiality; and (3) failure of the applicant to disclose the art or information resulting from an intent to mislead the PTO." *FMC Corp.*, 835 F.2d at 1415.

93. A party alleging inequitable conduct must show that "the withholding of information [meets the] thresholds of both materiality and intent." *Molins PLC*, 48 F.3d at 1178. "[M]ateriality does not presume intent, which is a separate and essential component of inequitable conduct." *Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567 (Fed. Cir. 1988). Once threshold levels of materiality and intent have been shown, a court must engage in "a careful balancing: when the misrepresentation or withheld information is highly material, a lesser quantum of proof is needed to establish the requisite intent. ... In contrast, the less material the information, the greater the

proof must be." *Purdue Pharma L.P. v. Endo Pharm.*, 438 F.3d 1123, 1129 (Fed. Cir. 2006) (internal citations omitted).

94. As to materiality, PTO regulations state that "information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or (2) It refutes, or is inconsistent with, a position the applicant takes in: (i) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability." 37 C.F.R. § 1.56(b) (1992).

95. "Intent need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequences of which are presumably intended by the actor." *Molins PLC*, 48 F.3d at 1180. Hence, while "materiality does not presume intent, which is a separate and essential component of inequitable conduct," *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1352 (Fed. Cir. 2002) (internal quotation marks and citation omitted), the materiality of a reference may lead to an inference of intent. *Bruno Indep. Living Aids, Inc.*, 394 F.3d at 1354 ("in the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information"). "Intent to deceive, however, cannot be 'inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent.'" *Purdue Pharma L.P.*, 438 F.3d at 1134.

96. Here, Defendants argue that the applicants for the '031 patent were guilty of inequitable conduct for (1) submitting affirmative misrepresentations to the PTO in the form of the Borchert Declaration and (2) failing to disclose the Machius reference.

a. *The Borchert Declaration*

97. According to Defendants, the applicants intentionally misrepresented the results of the Borchert experiment in order to prevent the examiner from reasserting an obviousness rejection over Suzuki and Bisgård-Frantzen. (D.I. 116 at 33-39.) First, Defendants argue that the applicants misrepresented the Borchert experiment's comparison with Suzuki because the temperature, preheating procedures, and calcium levels were different from Suzuki. (*Id*. at 34-35.) As discussed above (CL ¶ 66), I have concluded that the Borchert experiment, which directly compared the effect of the Suzuki deletion in BAN and BSG under the same conditions, was a fair way to address the obviousness question raised by the Suzuki reference. In addition, the experimental procedures were disclosed in the Borchert Declaration. (FF ¶¶ 44-45.) Thus, the applicants made no misrepresentations concerning the fairness of the comparison.

98. Second, Defendants argue that the applicants submitted results that they knew were unreliable because of the failure to account for the ramp-up period, the extrapolation beyond the last measurement, and the omission of data points. (D.I. 116 at 35-36.) Again, as discussed above, I have concluded that the ramp-up period and extrapolation problems do not materially affect the reliability of the results (CL ¶¶ 70-71), so there is no misrepresentation as to those issues.

99. Data points were removed prior to the calculation of half-lives (FF ¶ 46), and those omissions were not disclosed to the examiner (Borchert, Tr. at 386:20-22).

However, even assuming for the sake of argument that those omissions were material, to amount to inequitable conduct, they must have been made with the intent to deceive the PTO. *Molins PLC*, 48 F.3d at 1178. Here, Defendants have failed to show that the omissions were made to manipulate the results. Contrary to Defendants' assertions, Dr. Borchert and Ms. Holbo offered reasonable explanations for suspecting problems with the four omitted data points. (CL ¶ 72.) Certainly, omitting data believed to be suspect does not imply an intent to deceive. Thus, Defendants have failed to prove by clear and convincing evidence that the omissions were made with the intent that is necessary for inequitable conduct.

100. Third, Defendants argue that the applicants misrepresented the unexpectedness of their results. (D.I. 116 at 35.) Because of my conclusion that Defendants failed to show that the results were less than unexpected (CL ¶ 74-75), I also conclude that applicants made no misrepresentation about the unexpectedness of the Borchert experiment results.

101. Therefore, Defendants have failed to prove inequitable conduct related to the Borchert Declaration.

b. *Failure to Disclose the Machius Reference*

102. Defendants also argue that the applicants were guilty of inequitable conduct for failing to disclose the Machius reference to the examiner. (D.I. 116 at 29-33.)

103. Concerning the deletion claimed by the '031 patent, the Machius reference contains very little new information. (CL ¶ 79.) The reference predicts structural similarity between BSG and BAN, but that prediction is based on sequence

similarity that had already been disclosed by Bisgård-Frantzen. (*Id.*) The reference discusses the results from Suzuki and offers theories for why the thermostability was improved in BAN, but makes no predictions concerning the expected improvement in BSG. (FF ¶ 56.) The only relevant new information is the experimental result showing that the two amino acids to be deleted are found on a surface loop. (CL ¶ 79.) Thus, if the reference is material, it must be on that basis.

104. On the basis of the trial record, I conclude that the materiality of the Machius reference is marginal at best. The expectation of a similar result in BSG would mostly arise from the expected structural similarity between BSG and BAN, which was already in the art disclosed to the examiner. To that extent, the Machius reference is merely cumulative. As for the position of the deletions on a loop, it is difficult to see how such information would establish a prima facie case of unpatentability or would refute the applicants' position regarding patentability, especially given the applicants' strategy of providing experimental comparisons to the prior art. Thus, I conclude that the Machius reference is not highly material.

105. Importantly, Defendants have again failed to show by clear and convincing evidence that the failure to disclose the Machius reference was intended to deceive the PTO. Mr. Garbell and Dr. Borchert testified that they did not consider the reference to be material (Garbell, Tr. at 441:14-17, 442:5-21, 444:9-20; Borchert, Tr. at 414:21-415:4), and, given the reference's largely cumulative disclosure, that testimony is credible. While Dr. Borchert agreed that the reference disclosed some information not disclosed by Suzuki (Borchert, Tr. at 357:22-358:7, 359:12-360:7), that does not, contrary to Defendants' argument (D.I. 116 at 32), imply that Dr. Borchert considered it

material and knowingly withheld it. Also, while Mr. Garbell testified that he did not consider whether to cite the Machius reference (Garbell, Tr. at 442:5-21), that appears to be a result of the reference's marginal materiality rather than evidence of Mr. Garbell's intent to deceive.

106. Therefore, I conclude that Defendants have failed to prove inequitable conduct related to the Machius reference.

2. *Prosecution Laches*

107. Defendants final argument is that the '031 patent is unenforceable due to prosecution laches. (D.I. 115 at 90-91, ¶¶ 112-14.)

108. Prosecution laches is an equitable doctrine that may be applied to bar enforcement of patent claims following an unreasonable and unexplained delay in prosecution, even if the applicant technically complied with all pertinent statutes and rules. *Symbol Techs., Inc. v. Lemelson Med.*, 422 F.3d 1378, 1385, amended, 429 F.3d 1051 (Fed. Cir. 2005). Prosecution laches "should be applied only in egregious cases of misuse of the statutory patent system." *Symbol*, 422 F.3d at 1385. Egregious misuse means a "pattern of unjustifiably delayed prosecution" designed to extend the term of the patent. *Id*. At 1385-86.

109. According to Defendants, the doctrine should be applied here because the '031 patent issued approximately ten years after the effective filing date in 1995 and because the applicants intentionally delayed prosecution by responding to the examiner's first office action with narrowing amendments that were later withdrawn after the showing of unexpected results. (D.I. 115 at 90-91, ¶ 113.) Both arguments fail

because Defendants have not shown that the delay was an egregious misuse of the system. The prosecution history since 1995 shows a series of continuations and divisions. (FF ¶ 20.) As to almost all of that history, Defendants have failed to show anything unreasonable about that familiar course of prosecution. As for the response to the examiner's first office action in January 2004, I do find it troubling that Novozymes filed narrowing amendments that were motivated at least in part by a desire to delay the prosecution while experiments were conducted to justify broader claims. (*See* FF ¶¶ 34-36.) Nevertheless, that does not constitute an egregious case of delay that would justify holding the '031 patent unenforceable.

IV. SUMMARY OF CONCLUSIONS

For the reasons set forth herein, the disputed claim terms are construed as follows:

Claim Term	**The Court's Construction**
"*Bacillus stearothermophilus* alpha-amylase"	The court construes "*Bacillus stearothermophilus* alpha-amylase" to mean: "the functional enzyme product that is produced from the alpha-amylase gene of a *Bacillus stearothermophilus* organism."
"% homology"	The court construes "% homology" to mean: "a percent identity calculation according to the standard whereby the number of exactly matching amino acid residues in two sequences is compared to the total number of residue positions that are present in both sequences, expressed as a percent, e.g., as implemented by the GAP GCG program."

Defendants' Spezyme Ethyl infringes claims 1, 3, and 5 of the '031 patent; those claims are not invalid for obviousness or lack of enablement; and the '031 patent is not unenforceable due to inequitable conduct or prosecution laches.